REMARKS

Claims 35-39 are pending.

The Applicant addresses below the rejection made in the Office Action dated April 4, 2008, containing a final rejection.

The rejection under 35 U.S.C. §103(a)

Claims 35-39 were rejected for obviousness over WO 99/58478 (Claus) and WO 94/11337 (Arne).

The Applicants respectfully request reconsideration and withdrawal of this rejection. The major flaw in this rejection is the purported motivation cited for producing a low salt compound. According to the Office Action, motivation to produce a low salt compound arises because there is an expectation that decreasing the salt content would decrease side effects and undesirable properties. See the Office Action, page 3:

> One of ordinary skill in the art would be motivated to optimize the purity of the isolated product, lowering the salt content to less than 10% by weight, through routine and normal experimentation, with the reasonable expectation that a decrease in salt impurities would decrease side-effects and undesirable pharmacokinetic properties.

This argument is mistaken in general, i.e., when applied to compounds useful for pharmaceutical purposes in general. It is also mistaken in particular, i.e., when applied to the particular class of compounds being claimed.

In general, it is well known that there is no expectation that salts of pharmaceutical compounds are undesirable in terms of either side effects or other properties. Pharmaceutical

compounds are often prepared in the form of their salts in order to obtain some desirable property. See, e.g., U.S. Patent No. 6,936,718[1], col. 1, ll. 57-58: "Generally, pharmaceutical compounds are used as their pharmaceutically acceptable salts." See also *Pfizer, Inc. v. Apotex, Inc.*, 480 F. 3d 1348, 1353, 82 U.S.P.Q. 2d. 1321, 1324 (Fed. Cir. 2007): "Active drug molecules ... are frequently made into pharmaceutically-acceptable acid addition salts to improve their bioavailability." In fact, it is so well known as to need no citations to evidence that thousands of pharmaceutical compounds are used effectively as salts of one form or another.

Furthermore, Tolterodine®, which is structurally similar to the compounds recited in the present claims, has been marketed as the tartrate salt since 1998[2].

In particular, as applied to the compounds being claimed, the prior art taught away from the present claims since the prior art taught that compounds of the type being claimed should be used in the form of salts rather than as free bases.

U.S. Patent No. 6,858,650[3] teaches that compounds similar to those of the present claims, in their basic form, are disadvantageous. See col. 1, ll. 30-49:

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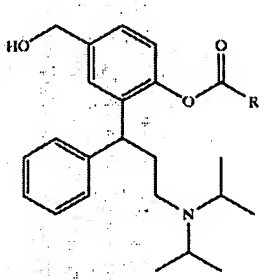
[1] A copy of U.S. Patent No. 6,936,718 is submitted with the Supplemental Information Disclosure Statement filed herewith.

[2] A copy of the approval letter for Tolterodine® tartrate is submitted with the Supplemental Information Disclosure Statement filed herewith.

[3] A copy of U.S. Patent No. 6,858,650 was submitted as Exhibit A with the Amendment filed November 27, 2007.

Formula A



in which R denotes C_1–C_6-alkyl, C_3–C_{10}-cycloalkyl or unsubstituted or substituted phenyl. These can occur in their optical isomers form as racemic mixtures and in the form of their individual enantiomers.

Compounds with the structure of formula A do, however, have low solubility in water. This restricts their oral bioavailability.

U.S. Patent No. 6,858,650 goes on to propose that the problems with these compounds can be overcome by the use of stable salt forms of the compounds. See col. 2, ll. 17-22:

> The problem for the present invention is therefore to provide highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, that avoid the stated disadvantages and are well suited to use in pharmaceutical-technical formulations and can be processed into these.

Thus, the teachings of U.S. Patent No. 6,858,650 that compounds of the type being claimed should be used in the form of salts is a teaching away from the claimed invention and is strong evidence that the claimed invention is non-obvious.

The Office Action cited Arne (page 6, line 37) and Claus (page 35, third paragraph, first two lines) as purportedly negating the impact of this teaching away.

The Applicants do not agree that Arne and Claus outweigh the teachings of U.S. Patent No. 6,858,650. The disclosures in Arne and Claus are mere "boilerplate" and would be understood as such by those skilled in the art. That is, Arne and Claus did not give serious consideration to whether the compound should be in the free base or the salt form but instead

merely recited the free base along with salts as theoretical possibilities. In contrast, U.S. Patent No. 6,858,650 (priority application filed 1999) reflects work done after Arne (published in 1994) and Claus (priority application filed 1998) which looked more carefully at the issue of free base versus salts. The extensive treatment that U.S. Patent No. 6,858,650 gave to this issue is discussed above. In view of these considerations, U.S. Patent No. 6,858,650 should be accorded greater weight on this issue than Arne or Claus.

Arne did not provide any motivation to reduce salt content. Instead, Arne taught that salts are desirable. Arne taught the transformation of compounds into mandelate salts (see page 13, line 16 to page 14, line 19). Furthermore, the pharmacological tests in Arne were done using salts (see page 14, lines 20-33).

Thus, there was no motivation to reduce the salt content of the claimed compounds to the recited level of less than 10% by weight.

Moreover, the Applicants continue to believe that the claimed invention shows unexpected results. The present application discloses that the salts of the prior art and the claimed compounds were formulated into compositions suitable for transdermal delivery. When the salts of the prior art were then compared with one of the claimed compounds for their transdermal flux rates, it was found that the claimed compound, in highly pure free base form, with less than 10% salt content by weight, was vastly superior to the prior art compounds. See paragraphs 116-118 and Table 2 of U.S. Patent Publication No. 2006/0014832 (the publication of the present application):

> **[0116]** It is preferable that the high purity compound of the general Formula Ibe present in the form of the free base with a combined salt part of less than 10 percent by weight, especially preferable less than 5% or 3%, notably especially preferable less than 1%.

[0117] If the high purity salts from 3,3-diphenylpropylamine derivates known from WO 01/35957, for example, the fumarate salt from fesoterodine, only lead in the case of transdermal delivery to flux rates not sufficient for transdermal treatment, even the addition of loaded molecules such as silicates or Chitosan, for example, or of skin penetration amplifiers like oleic acid or PGML (polyglycol monolaurate) to the matrices containing the active ingredient salt does not lead to satisfactory flux rates (Table 2).

[0118] Even an in-situ release of the base from the corresponding salt through the addition of calcium silicate during manufacture of the adhesive matrix, as described in WO 94/07486, does not lead to the flux rates through the human skin desired (Table 2), because the in-situ conversion to the free base is generally not absolute so that too high a proportion of the active ingredient in its protonated form is present in the matrix.

TABLE 2

Lot-No	Contact adhesive	Procedure	Loading of the active ingredient (Percent by weight fesoterodine)	Matrix weight (g/m^2)	Flux $\mu g/cm^2/Day$ (in steady state; after 24 hours) Mouse Skin	Human skin
20111080[1]	Acrylate	Solvent	15	100	705	n.d.
20302060[2]	Acrylate	Solvent	15	87	n.d.	332.64
20111085[1]	EVA	Hot melt	15	84	510	323.7
20111086[1]	Silicone	Hotmelt	15	63	495	n.d.
20302062[2]	Silicone	Hotmelt	15	100	n.d.	544.89
20111087[1]	SxS	Hotmelt	15	89	460	383.8
20302063[3]	Silicone + PVAc[6]	Hotmelt	15	83	n.d.	501.09
20002031[2]	Acrylate	Solvent	15 Fumarate	105	27	n.d.
20104033[2,3]	Acrylate/OL	Solvent	15 Fumarate	110	84	n.d.
20106061[4]	Silicone	Solvent	15 Fumarate	60	n.d.	24,2
20106043[5]	Silicone	Hotmelt	15 DiOH[5]	101	n.d.	2,3

n.d. = not determined;

[1]= fesoterodine was added to the matrix as the free base;

[2]= Comparison example manufactured through the use of fesoterodine-fumarate salt;

[3]= Comparison example manufactured through the use of fesoterodine-fumarate salt with oleic acid as the permeation enhancer;

[4]= Comparison example manufactured through the in-situ release of the base from the fumarate salt into the adhesive matrix;

[5]= Comparison example manufactured through the use of the dihydroxymetabolites (2-[3-(1,1-diisopropylamino)-1-phenylpropyl]-4-(hydroxy methyl)phenol) from fesoterodine;

[6]PVAc = Poly Vinyl Acetate.

The Office Action did not agree with the Applicants' position that the above disclosure demonstrates unexpected results. According to the Office Action, a comparison has not been made with the closest prior art. The Office Action argued that the closest prior

art is the hydrochloride salt disclosed in Arne rather than the fumarate salt used in the Applicants' comparison.

The Applicants believe the Office Action is mistaken. The fumarate salts used by the Applicants are compounds that, except for their salt content, fall within the scope of the structural formula recited in present claim 35. The hydrochloride salts disclosed in Arne are compounds that, even ignoring their salt content, fall outside the scope of the structural formula recited in present claim 35.

See page 1, lines 18-27, of Arne, where the structure of formula I and the definition of R^1 mean that the compounds of Arne cannot satisfy the structural formula recited in the present claims. There is no possibility in Arne for the presence of the carbonyl group attached to the R group in the structural formula recited in present claim 35.

It should go without saying that the closest prior art should be a compound that has the same chemical structure as the claimed compound. Thus, the Applicants' fumarate salts, since they have a structure within the scope of the structural formula recited in present claim 35, are closer than Arne's hydrochloride salts, which have a structure outside the scope of the structural formula recited in present claim 35.

In view of the above, it is respectfully requested that this rejection be withdrawn.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with the filing of this paper, or any defect seen to be remaining in this application after the filing of this paper. The Commissioner is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully Submitted,

Date: November 5, 2008

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CUSTOMER NUMBER 26646